Notice of Allowability	Application No.	Applicant(s)	
	10/670,135	XU ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the interview conducted 3 March 2005*.

2. ☒ The allowed claim(s) is/are *1,2,4-10 and 76-80*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 3/29/2004
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Cancel claim 3.

Amend claims 1, 2, 4 and 8-10 thus:

1. (Amended) An isolated nucleic acid consisting ~~essentially~~ of the nucleic acid sequence of SEQ ID NO: 1, or the complement thereof.
2. (Amended) An isolated nucleic acid consisting ~~essentially~~ of the nucleic acid sequence of SEQ ID NO: 2, or the complement thereof.
4. (Amended) A method for producing a ~~GrB-NIC~~ non-immune cell granzyme B (GrB-NIC) polypeptide, comprising:

   (a) transforming or transfecting a host cell with a nucleic acid comprising the nucleic acid sequence of SEQ ID NO: 1, to obtain a transformed or transfected host cell;

   (b) culturing the transformed or transfected host cell to obtain a cell culture; and,

   (c) expressing the nucleic acid in the transformed or transfected host cell;

   thereby ~~to produce~~ producing the GrB-NIC polypeptide.
8. (Amended) The method of claim 7, wherein said regulatory elements comprise native GrB-NIC regulatory elements within the nucleic acid sequence set forth in SEQ ID NO:1 from position 1 through position 1031.
9. (Amended) A vector comprising a cloned nucleic acid, said cloned nucleic acid consisting ~~essentially~~ of the nucleic acid sequence of SEQ ID NO: 1 or complement thereof.

10. (Amended) A vector comprising a cloned nucleic acid, said cloned nucleic acid consisting ~~essentially~~ of the nucleic acid sequence of SEQ ID NO: 2 or complement thereof.

Add the new claims 76-78.

76. (New) The method of claim 4, further comprising isolating the GrB-NIC polypeptide from the host cell or cell culture.
77. (New) The vector of claim 10, further comprising regulatory nucleotide sequence elements necessary to express the encoded GrB-NIC polypeptide in a eukaryotic host cell.
78. (New) The vector of claim 77, wherein said regulatory nucleotide sequence elements comprise native GrB-NIC nucleotide sequence elements within the nucleic acid sequence set forth in SEQ ID NO:1 from position 1 through position 1031.
79. (New) A vector comprising a cloned nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 3 and further comprising regulatory nucleotide sequence elements necessary to express the encoded GrB-NIC polypeptide in a eukaryotic host cell.
80. (New) The vector of claim 79, wherein said regulatory nucleotide sequence elements comprise one or more native GrB-NIC nucleotide sequence elements within the nucleic acid sequence set forth in SEQ ID NO:1 from position 1 through position 1031.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Stephen M. Hash on 3 March 2005.

The following is an examiner's statement of reasons for allowance:

The subject matter described by claims 1, 2, 4-10 and 76-78 allowed herein is enabled by, and adequately disclosed in, the specification, see, e.g., Figure 1 depicting

numerous native GrB-NIC regulatory nucleic acid sequence elements, Tables 1 and 2 which indicate alternative regulatory nucleic acid sequence elements, and paragraphs 0007-0008, 0012, 0019, 0109-0130.

The subject matter of the allowed claims is free of the prior art of made of record herewith wherein there is no disclosure, no teaching, and no suggestion of the 1,977-nucleotide sequence of SEQ ID NO:1 herein, or the 946-nucleotide sequence of SEQ ID NO:2 described by claims 1 and 2 as amended above, sequences that are required by claims 4-10 and 76-78 depending therefrom. Wargnier et al., made of record with Applicant's Information Disclosure filed 29 March 2004, fails to suggest that the 5'-terminal sequence of 1,031 nucleotides of SEQ ID NO:1 should be encoded with a granzyme B-encoding nucleic acid sequence because the most 3'-proximal regulatory element they investigate, see Figure 3, is present in a region that commences 970 nucleotides upstream from the 3'-terminus of SEQ ID NO:1 herein. The closest prior art to SEQ ID NO:1, Hanson et al., 1990, made of record herewith, exceeds the 5'-terminus of SEQ ID NO:1 by an additional 73 nucleotides and has a relative deletion of five contiguous nucleotides corresponding to the sequence CCAAT at positions 387-381 of SEQ ID NO:1. In addition to these differences, neither Hanson et al. nor the rest of the prior art made of record herein suggests that even the nucleotide sequence region that Hanson et al. define should be combined as a regulatory sequence region with the upstream 875-nucleotides set forth in the sequence of SEQ ID NO:1 herein.

Instead, the prior art teaches away from the preparation of a nucleotide sequence having the 3'-terminal sequence shared by both SEQ ID NO:1 and SEQ ID NO:2 herein, where there is no coincident terminal sequence in any prior art polynucleotide. The nucleotide sequences of Figure 3 of Schmid et al., 1987, and of Figure 1 of Klein et al., 1989, both made of record with Applicant's Information Disclosure Statement of 29

March 2004, lack the 5' nucleic acid sequence elements present in the region from position 1 through position 1032 of SEQ ID NO:1 and Figure 1 herein. Schmid et al. fail to disclose the 5'-proximal coding elements specifying the 34 amino proximal amino acids of the long form of human granzyme B encoded by SEQ ID NO:2 herein. While the nucleic acid sequence of Figure 1 Klein et al., 1989, comprises all of the coding regions of SEQ ID NO:2 herein, Klein et al. do not disclose a nucleic acid sequence either consisting of SEQ ID NO:1 herein or consisting of SEQ ID NO:2 herein because their genomic DNA sequence divides the coding sequence for human granzyme B with four, non-coding, intron nucleotide sequences. Neither can Klein et al. suggest the preparation of a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:3 herein because they fail to appreciate that the sequence of 102 nucleotides 5'-adjacent to the initiation codon they choose as the beginning of their exon 1 encodes any part of a human granzyme B polypeptide.

As was the case with Schmid et al., both Figure 1 of Trapani et al., 1988, and Figure 1 of Caputo et al., 1988, both made of record herewith, fail to disclose the 5'-proximal coding elements specifying the 34 amino proximal amino acids of the long form of human granzyme B encoded by SEQ ID NO:2 herein. Similarly, both SEQ ID NO:1309 of Cocks et al., US 6,607,879, and SEQ ID NO:8 of Tataki et al., US 6,537,784, both made of record herewith, fail to disclose the 5'-proximal coding elements specifying the 34 amino proximal amino acids of the long form of human granzyme B encoded by SEQ ID NO:2 herein. As was the case with Klein et al., 1989, Figure 3 of Haddad et al., 1990, and Figure 2 of Caputo et al., 1990, both made of record herewith, fail to disclose or suggest a nucleic acid sequence consisting of SEQ ID NO:1 herein, or consisting of SEQ ID NO:2 herein, because their genomic DNA sequences divide the nucleotide sequence encoding human granzyme B with sequences of four non-coding introns and,

because they also fail to appreciate that the sequence of 102 nucleotides 5'-adjacent to the initiation codon both choose as the beginning of their exon 1 encodes any part of a human granzyme B polypeptide, neither Haddad et al. nor Caputo et al., 1990, suggest the preparation of a nucleic acid sequence consisting of SEQ ID NO:2 or encoding the nucleic acid sequence of SEQ ID NO:3 herein.

While each of Klein et al., Haddad et al., and Caputo et al., 1990, disclose, but do not recognize, polynucleotides comprising the 843-nucleotide open reading frame within SEQ ID NO:2 herein, two publications in the prior art, Dahl et al., 1990, and Rosenblum et al., US 2003/0086919, both made of record herewith, disclose an open reading frame present in the human granzyme B gene encoding the 281-amino acid sequence of the long form of human granzyme B, termed the non-immune cell granzyme B herein, set forth in SEQ ID NO:3 herein. See SEQ ID NO:13 of Rosenblum et al. and Figure 2 of Dahl et al. Yet both Dahl et al. nor Rosenblum et al. fail to disclose or suggest a nucleic acid sequence having the further, 3'-proximal, sequence of 103 nucleotides within SEQ ID NO:2 thus cannot render obvious the subject matters of claims 2, 10, 77 or 78.

Neither do Dahl et al. or Rosenblum et al. suggest the preparation of an expression vector of claims 79 and 80 above comprising a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:3 in a context for recombinant expression of the encoded non-immune cell granzyme B because both teach away from the preparation of such a vector. Rosenblum et al. cannot render claims 79 or 80 obvious because they teach that only a nucleic acid sequence encoding the 229-amino acid sequence of the mature granzyme, with an inserted enterokinase cleavage site, fused to a heterologous polypeptide should be placed in a vector to permit expression of the fusion polypeptide. Dahl et al. teach away from the preparation of vectors of claims 79 and 80 because, while they suggest, pages 468-469, that properties of what they consider an abnormal

52-amino acid signal peptide are worthy of "current[ ] investigat[ion]", neither they nor any teaching in the intervening thirteen years suggest that any investigation involved the preparation of a vector for recombinant expression of a nucleic acid sequence encoding the long form of granzyme B having the amino acid sequence of SEQ ID NO:3. Indeed, the intervening publications of the prior art made of record herewith show that discovery and recombinant expression of nucleic acid sequences encoding divergent forms of the amino acid sequence of the mature granzyme B, and new granzyme proteases, was the foremost motivation experienced by those of ordinary skill in the art at the time the invention was made.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone number for all communications for the organization where this application or proceeding is assigned is now 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
3 March 2005

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